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# Solid-Phase Synthesis of Cleavable *N*-Arylmaleimides: Applications in 1,3-Dipolar Cycloaddition and in Thiol Scavenging

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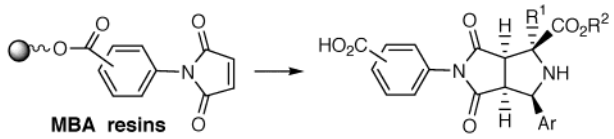
## ABSTRACT




**An efficient solid-phase synthesis of polymer-supported *N*-arylmaleimides has been developed. Various *N*-arylmaleimidobenzoic acids (MBA) were elaborated onto Rink and SASRIN resins by reaction of the aniline precursors with maleic anhydride followed by facile cyclative dehydration of the resulting maleimic acids. Applications of these acid-cleavable MBA resins in the solid-phase synthesis of highly decorated pyrrolidines and as thiol scavengers are presented.**

Even though maleimides are highly prized substrates in synthetic organic chemistry (as dienophiles, dipolarophiles, and Michael acceptors), and although they find abundant utility in a variety of biological applications,[2] no reports on the preparation of *cleavable* polymer-supported *N*-substituted maleimides have yet appeared in the literature (cf. Figure 1).[3] The use of Friedel−Crafts reactions to attach a maleimide moiety to unfunctionalized polystyrene, providing *N*-methylmaleimido polystyrene, has long been precedented in the polymer chemistry literature[4] and has recently been revisited by Porco and co-workers.[5,6] This approach, however, does not readily lend itself to the preparation of *cleavable* maleimide resins. We became initially interested in the preparation of acid-cleavable supported maleimides as part of an effort to apply our previously reported tandem aza-[4 + 2]/allylboration chemistry[7] onto solid support. The potential utility of supported maleimides in solid-phase organic synthesis and/or as scavengers in parallel solution-phase synthesis has prompted us to disclose their preparation. We also report herein on applications of these cleavable resin-supported maleimides in diastereoselective 1,3-dipolar cycloaddition chemistry and thiol scavenging.

Our initial efforts were directed at synthesizing *N*-aminoalkylmaleimides via dehydrative cyclization of *N*-alkylmaleimic acid intermediates attached to trityl resin (**1** → **2** in Scheme 1).[8] The reaction of resin-bound amines with maleic (or succinic) anhydrides cleanly afforded the desired *N*-alkylmaleimic acids (or *N*-alkylsuccinamic acid). However, all of the attempted solid-phase[6] and solution-phase methods[9] used for dehydrative cyclization of such an intermediate

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(2) See, for example: (a) Janda, K. D.; Ashley, J. A.; Jones, T. M.; McLeod, D. A.; Schloeder, D. M.; Weinhouse, M. I. *J. Am. Chem. Soc.* **1990**, *112*, 8886. (b) Smyth, G. E.; Colman, R. F. *J. Biol. Chem.* **1991**, *266*, 14918. (c) Rusiecki, V. K.; Warne, S. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 707. (d) Hermanson, G. T. *Bioconjugate Techniques*; Academic Press: New York, 1996; p 148. (e) Seelig, B.; Keiper, S.; Stuhlmann, F.; Jäschke, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4576.

(3) Most recently, a method to anchor maleimide to trityl resin was reported: Barrett, A. G. M.; Boffey, R. J.; Frederiksen, M. U.; Newton, C. G.; Roberts, R. S. *Tetrahedron Lett.* **2001**, *42*, 5579.

(4) Stevens, M. P.; Jenkins, A. D. *J. Polym. Sci.* **1979**, *17*, 3675.

(5) Wang, X.; Parlow, J. J.; Porco, J. A. *Org. Lett.* **2000**, *2*, 3509.

(6) For another preparation from aminomethyl polystyrene and maleic anhydride using dehydrative cyclization, see: Rebek, J., Jr.; Gaviña, F. *J. Am. Chem. Soc.* **1975**, *97*, 3453.

(7) Tailor, J.; Hall, D. G. *Org. Lett.* **2000**, *2*, 3715.

(8) For a comprehensive overview, see: *Maleic Anhydride*; Trivedi, B. C.; Culberton, B. M.; Plenum Press: New York, 1982.

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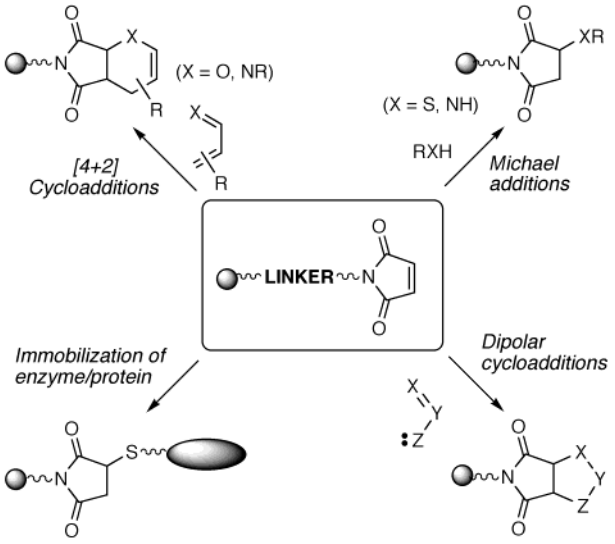
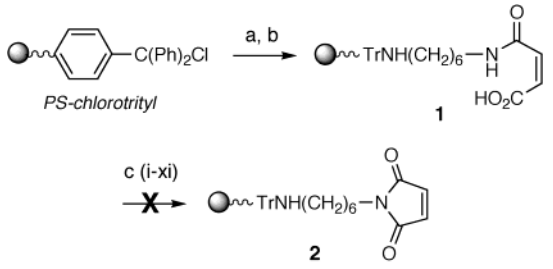



**Figure 1.** Potential applications of polymer-supported maleimides in solid-phase chemistry.

**Scheme 1.** Attempted Cyclative Dehydration Routes to Cleavable Resin-Supported *N*-Alkylmaleimides[a]

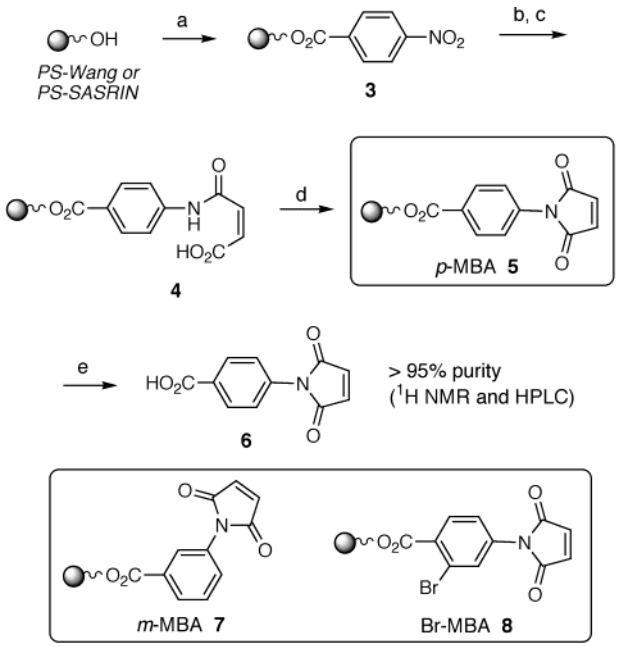



[a] (a) $H_2N(CH_2)_6NH_2$ (50 equiv), THF, rt, 2 h. (b) Maleic anhydride (20 equiv), $CH_2Cl_2$. (c) Conditions attempted at rt: (i) $Ac_2O$/NaOAc (cat.); (ii) DIC; (iii) DIC, DMAP; (iv) TEA; (v) pyridine; (vi) HBTU; (vii) $Ti(i\text{-}OPr)_4$; (viii) TMOF; (ix) TMOF, DMAP; (x) $SOCl_2$, pempidine; (xi) $(COCl)_2$, pempidine.

failed to cleanly furnish the resin-bound maleimide (see footnote c in Scheme 1). Experimental conditions that required acidic conditions or extensive heating periods at highly elevated temperatures were not attempted (incompatible with a trityl linker). Similarly, Mitsunobu coupling between resin-bound alcohols[10] and maleimide, as well as milder variants of the Gabriel reaction[11] to displace a resin-immobilized primary mesylate were found to be ineffective.

*N*-Arylmaleimidobenzoic acids (MBA) are frequently employed in the preparation of (maleimide) cross-linked polymers.[12] We decided to examine that chemistry for the solid-phase synthesis of acid-cleavable MBA-conjugated resins. To our satisfaction, this synthetic route (Scheme 2)

**Scheme 2.** General Route for the Preparation of *N*-Arylmaleimidobenzoic Acid (MBA) Resins[a]




[a] (a) *p*-Nitrobenzoic acid (8 equiv), DIC (4 equiv), DMAP (cat.), DMF, rt, 2 h (repeated twice). (b) $SnCl_2 \cdot 2H_2O$ (20 equiv, 2 M in anhydrous DMF), DMF. (c) Maleic anhydride (20 equiv), DMF, rt, 6 h. (d) $Ac_2O$ (10 equiv), NaOAc (1 equiv), DMF, rt, 4 h. (e) Wang resin: 90% TFA/$CH_2Cl_2$. SASRIN resin: 0.5% TFA/$CH_2Cl_2$.

indeed provides an efficient protocol for the attachment of *N*-arylmaleimides onto acid-cleavable supports such as Wang or SASRIN resins. For example, coupling of the readily available *p*-nitrobenzoic acid (or substituted analogues) using DIC/DMAP (cat.), followed by $SnCl_2$ reduction of the nitro group in **3**, and the attendant coupling of the unmasked aniline functionality to maleic anhydride cleanly furnished the supported *N*-arylmaleimic acid **4**. Dehydrative cyclization of **4** was readily effected by treatment of the resin with acetic anhydride (10 equiv) and sodium acetate (1 equiv) for 4 h at *room temperature*, in anhydrous DMF, to obtain the desired *p*-*N*-arylmaleimidobenzoic acid (*p*-MBA) resin **5** (Scheme 2).[13] The efficiency of this procedure was monitored by cleavage of resin samples with TFA/$CH_2Cl_2$ and analysis of the resulting maleimide **6** by NMR and LCMS.[14] It is

(9) For examples of solution-phase synthesis of maleimides, see: (a) Tawney, P. O.; Snyder, R. H.; Conger, R. P.; Leibbrand, K. A.; Stiteler, C. H.; Williams, A. R. *J. Org. Chem.* **1961**, *26*, 15 and references therein. (b) Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 439 and references therein. (c) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, W. O. *J. Org. Chem.* **1991**, *56*, 5893 and references therein. (d) Braish, T. F.; Fox, D. E. *Synlett* **1992**, 979. (e) Clevenger, R. C.; Turnbull, K. D. *Synth. Commun.* **2000**, *30*, 1379.

(10) (a) Walker, M. A. *Tetrahedron Lett.* **1994**, *35*, 665. (b) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.

(11) (a) Landini, D.; Rolla, F. *Synthesis* **1976**, 389. (b) Sato, T.; Otera, J. *Synlett* **1995**, 336.

(12) (a) Stenzenberger, H. In *Polyimides*; Wilson, D., Stenzenberger, H. D., Hergenrother, P. M., Eds.; Blackie: Glasgow, 1990; p 79. (b) Liu, F. J.; Munukutta, S.; Levon, K.; Tesoro, G. *J. Polym. Sci., Part A: Polym. Chem.* **1992**, *30*, 157 and references therein.

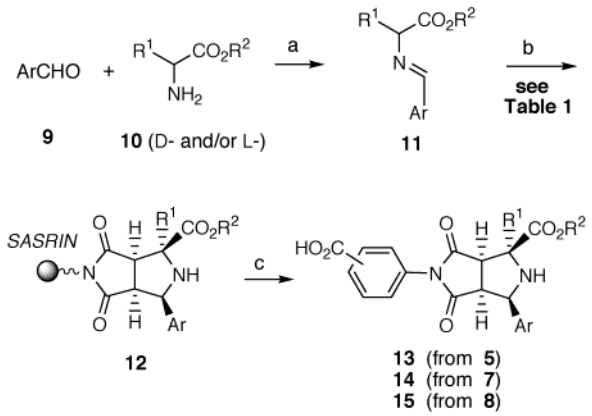
(13) In stark contrast, use of DIC/DMAP procedures for the cyclization step was unsuccessful, giving a complex mixture of products.

noteworthy that by the same analytical criteria, the direct attachment of preformed *p*-MBA (via ester or amide linkages) provided us with cleaved products of lower purity. The corresponding isomeric *m*-MBA resin **7** and a bromo-derivatized MBA resin (**8**) were also made to show the generality of this approach.[14] In principle, the phenyl ring on these MBA resins could be further diversified by, for instance, Suzuki or Heck coupling on brominated resin **8**.

Maleimides have already found use in the solid-phase synthesis of fused bicyclic pyrrolidines,[15] most commonly via the 1,3-dipolar cycloaddition[16,17] of azomethine ylids generated from α-aminoesters and aldehydes. To date, however, because of the lack of methods to access *cleavable* resin-supported maleimides, another one of the highly diversifiable building blocks has always been sacrificed as the resin-immobilized component. For instance, Hamper and co-workers opted to use the Mitsunobu coupling of substituted hydroxybenzaldehydes to immobilize the aldehyde reagent onto the solid support.[15a] Hird and Bicknell, on the other hand, took advantage of commercially available amino acid loaded resins to access azomethine ylids.[15b]

To explore the utility of our MBA resins, we chose to study their usefulness in intermolecular 1,3-dipolar cycloaddition chemistry with azomethine ylids (Scheme 3). After

**Scheme 3.** 1,3-Dipolar Cycloaddition between Azomethine Ylids of α-Iminoesters **11** and SASRIN MBA Resins **5**, **7**, and **8**[a]




[a] (a) Toluene, 80 °C, 1 h. (b) α-Iminoester (10 equiv), DBU (5 equiv), LiBr (5 equiv), SASRIN-MBA resin **5**, **7**, or **8** (1 equiv), THF, rt, 1 h. (c) 0.5% TFA/$CH_2Cl_2$, rt, 1 h.

examining a variety of Lewis acid/base combinations following the methods of Grigg[16a] and/or Tsuge,[18] we opted for Tsuge's *N*-metalation route, which is an established method for the stereocontrolled synthesis of functionalized pyrrolidines in solution phase (Scheme 3). Thus, an equimolar mixture of LiBr and DBU in dry THF (5-fold excess relative to initial loading of resin), in the presence of the Schiff base (10-fold excess) and the SASRIN *p*-MBA resin **5**, furnished after cleavage (0.5% TFA in $CH_2Cl_2$) the *syn-endo* diastereomer of the cycloadduct, as expected, after only *1 h at room temperature*. The use of anhydrous conditions was found necessary mainly to thwart the hydrolysis of the resulting imide moiety. The mild conditions of Tsuge's *N*-metalation route employed herein (ambient temperature, 1 h) are in vivid contrast to the previously reported solid-phase approaches (100−110 °C, 18−24 h).[15a,b] On the other hand, the high diastereoselectivity obtained using such mild conditions is well precedented in 1,3-dipolar cycloaddition reactions both in solution and on solid phase. Our assignment of the relative stereochemistries is consistent with that reported in solution chemistry, resulting from the *endo* addition of the maleimide to the *syn*-W (*E*,*E*-ylid) configuration of the azomethine ylid, and is supported by NOE difference studies.

A number of 1,3-dipolar cycloadducts (**13**, **14**, **15**) of the respective SASRIN MBA resins (**5**, **7**, **8**) were prepared in order to make a preliminary assessment of the scope and limitations of our solid-phase synthetic strategy to substituted pyrrolidines (Table 1). The general structure−reactivity

**Table 1.** Preparation of Substituted Pyrrolidines **13**−**15** from **11** and SASRIN MBA Resins (**5**, **7**, **8**) According to Scheme 3[a]

| entry | aldehyde (Ar) | α-iminoester ($R^1$, $R^2$) | product | yield[b] (%) | purity[c] (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | Leu (*i*-Bu, Me) | **13a** | 85 | >90 |
| 2 | 3,4,5-(MeO)$C_6H_2$ | Leu (*i*-Bu, Me) | **13b** | 50 | 90 |
| 3 | $C_6H_5$ | Tyr (*p*-HO-Bn, Et) | **13c** | 95 | >80 |
| 4 | 3-$NO_2C_6H_4$ | Phe (Bn, Et) | **13d** | 80 | >90 |
| 5 | $C_6H_5$ | Phe (Bn, Et) | **13e** | 65 | >90 |
| 6 | 2-furyl | Phe (Bn, Et) | **13f** | 80 | >90 |
| 7 | 1,3,5-(Me)$C_6H_2$ | Ala (Me, Et) | **13g** | | |
| 8 | $C_6H_5$ | His ($CH_2$-4-Im, Et) | **13h** | | |
| 9 | 3-$NO_2C_6H_4$ | Phe (Bn, Et) | **14a** | 80 | 95 |
| 10 | 3-$NO_2C_6H_4$ | Phe (Bn, Et) | **15a** | 55 | >90 |
| 11 | 2-furyl | Phe (Bn, Et) | **15b** | 75 | >90 |

[a] Reactions were conducted according to Scheme 3 (typical scale 0.1−0.5 g resin). See Supporting Information for detailed conditions. [b] Nonoptimized weight yields of crude products, isolated as monotrifluoroacetate salts after cleavage from the resin. [c] Estimated by integration of $^1$H NMR signals.

trends, based on the limited examples reported herein, may be summarized as follows: (i) The cycloaddition reaction

(14) The resin loading was estimated by combustion analysis of the nitrogen content on the resin, and the results indicated a loading in excess of 90% in the cases of all three linkers reported herein. Estimated values of resin loading and homogeneity of cleaved maleimides were also assessed from nonoptimized weight yields after acidic cleavage (characterized by NMR, and LCMS): *p*-MBA, 100%; *m*-MBA, 90%; Br-MBA, 70%).

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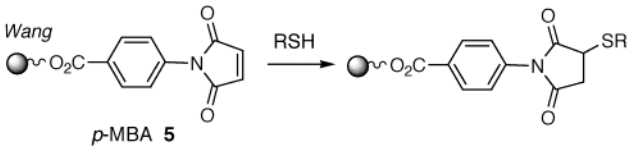
(17) For other recent applications of 1,3-dipolar cycloaddition on solid support, see: (a) Costero, A. M.; Pitarch, M.; Luz Cano, M. *J. Chem. Res., Synop.* **1994**, 316. (b) Murphy, M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029. (c) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1996**, *2*, 207. (d) Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157. (e) Peng, G.; Sohn, A.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 8342.

**Scheme 4.** Scavenging of Sulfydryl Compounds with Wang *p*-MBA Resin **5**[a]




| RSH | % scavenged 45 min | 6h | 18h |
|---|---|---|---|
| HO, SH | 70 | 95 | > 98 |
| O, SH | 75 | 90 | > 98 |
| SH | 70 | > 98 | > 98 |

[a] These experiments were conducted in deuterated chloroform (rt), and the amount of thiol or thio acid left in solution was quantified by integration of signals by $^1$H NMR.

is more sensitive to the steric bulk on the azomethine ylid than the electronic factors, i.e., electron-rich and electron-poor Schiff bases underwent the 1,3-dipolar cycloaddition with comparable efficiency (entries 2 and 4), whereas the sterically encumbered mesitaldehyde-derived Schiff base (entry 7) failed to undergo the cycloaddition under the same conditions. (ii) Amino acid building blocks with side chains bearing an unprotected basic moiety, such as the imidazole ring in histidine (entry 8), did not furnish clean cycloaddition products under these conditions; those with an unprotected acidic side chain (entry 3) did yield the desired cycloadduct, albeit in lower purity.

With the increased application of combinatorial synthetic protocols in solution, there is also a greater need for various scavengers and solid-support immobilized reagents.[19] Maleimide resins may be used in scavenging excess 1,3-dipoles, dienes,[5] and thiols in solution (cf. Figure 1). While the use of a maleimide resin as a scavenger in the form of a cycloaddition partner has garnered attention,[5] its utility as a thiol scavenger has not. Solid-support immobilized maleimide moiety readily undergoes Michael addition with thiol nucleophiles. Thus it functions as a thiol scavenger in solution *without* generating any acidic byproducts, unlike the case when solid-support immobilized alkylhalides are used as scavengers. The reaction of three model sulfydryl compounds (2-mercaptoethanol, thioacetic acid, thiophenol) with a 2-fold excess of the Wang *p*-MBA resin **5** (1.3 mmol/g loading) was found to be reasonably efficient, providing quantitative thiol removal as observed by $^1$H NMR after 18 h (rt, chloroform). We expect that more efficient scavenger resins (i.e., higher loading) could easily be prepared using, for instance, a polyamine tether to increase the density of maleimides on the resin.

In conclusion, we have developed conditions for the first general approach to the solid-phase synthesis of acid-cleavable *N*-arylmaleimidobenzoic acid (MBA) resins. Such a strategy can be used for more diversity-effective approaches to combinatorial libraries of heterocycles using diastereoselective 1,3-dipolar cycloaddition chemistry. We have also demonstrated the potential utility of maleimide resins for use as "neutral" thiol scavengers.

**Acknowledgment.** This work was funded by the Natural Sciences and Engineeering Research Council (NSERC) of Canada and the University of Alberta.

**Supporting Information Available:** Experimental procedures for the synthesis of *N*-arylmaleimide resins, 1,3-dipolar cycloadducts, and thiol scavenging; characterization data (NMR, MS) along with copies of $^1$H and $^{13}$C NMR spectra for pyrrolidines **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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